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(54) Ionic dressing for topical administration of drugs to wounds and burns.

(57) Novel wound dressings are provided herein. The wound dressing includes a substrate and a physiologically- or biologically- active agent adsorbed therein. The substrate is chemically modified to have ionic-adsorbing sites thereon. The agent is in its ionic form. Upon contact with body exudate from wounds to which such wound dressing is applied, the physiologically- or biologically- active agent is released in a controlled manner by ion exchange with the ions in the body exudate in proportion to the amount of exudate.

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IONIC DRESSING FOR TOPICAL ADMINISTRATION OF DRUGS TO WOUNDS AND BURNS

This invention relates to ionic forms of dressings to which a variety of ionic, physiologically- and/or biologically-active materials can be adsorbed so that a controlled release of that material into body exudates of wounds can take place.

When drugs are systemically administered to treat wounds (including cuts, abrasions, incisions, ulcers and infected wounds or burns), a large portion of the drugs is either degraded or adsorbed by nontarget tissues and only a small portion of the initial dose reaches the target site. The efficiency of systemic dosing is further decreased in the trauma patient (as in accidents, earthquakes, fires and wars) who often suffer a decreased vascular flow and thus have reduced drug circulation. Furthermore, the trauma patient often fails to provide information regarding sensitivity to drugs, or fails to take drugs orally. Topical drug administration, in theory, would provide immediate, direct, and sustained effects at the target site, and reduce side-effects and degradation of drugs encountered in systemic dosing. Topical application also permits rapid removal and replacement of drugs when adverse effects are noticed. When cleansing is not readily available, topical application is more effective in destroying microbial spores because a higher concentration of drugs can be applied. Thus, treatment of wounds or burns will benefit from an improvement of topical administration, whether used alone or in conjunction with systemic dosing.

Currently, antibiotics, e.g. fusidic acid, chlorohexidine, Neomycin, Polymyxin and Bacitracin are topically applied in gel, cream or ointment forms (occasionally in aerosol and powder). Because a high concentration of the drugs are in direct contact with the target tissue, some of the drugs cause allergic reaction by contact with the target tissue, some of drugs cause allergic dermatitis, particularly in patients with stasis ulcers or eczema, or exhibit toxicity.

To provide a controlled release of drugs, a U.S. Army medical team has developed microcapsules (diameters of <10 µ) containing ampicillin for topical application to wound sites.

The art is replete with patents involving the absorption or absorption of drugs on carriers. Among them are the following:

Canadian Patent No. 486,203 to Johnson & Johnson
Canadian Patent No. 503,389 to Casumano
Canadian Patent No. 823,628 to Wyant
Canadian Patent No. 547,091 to Lerner
Canadian Patent No. 588,169 to Chicopee
Canadian Patent No. 839,229 to Astra
Canadian Patent No. 1,049,407 to Pharmacia
U.S. Patent 2,381,621 patented August 7, 1945 by Wallace & Teiman Products, Inc.
U.S. Patent No. 2,804,425 patented August 27, 1957 by American Cyanamid Company
U.S. Patent No. 3,817,702 patented June 18, 1974 by Bayer Aktiengessellschaft
U.S. Patent No. 3,987,793 patented October 26, 1976 by Ethicon Inc.
U.S. Patent No. 4,549,011 patented October 22, 1985 by Orgenics Ltd.
U.S. Patent No. 4,585,652 patented April 29, 1986 by Regents of the University of Minnesota

Enzymes, e.g. fibrinolytic proteases and deoxyribonucleases, are occasionally used to dissolve fibrous or purulent accumulations in infected wounds or burns. These enzymes are currently applied in the form of gels (e.g., carboxymethyl cellulose gel) or ointments. Such systems may suffer the same problems of allergy and time-consuming application described above. Furthermore, they do not provide mechanisms for removal of enzymic hydrolysates wich are potential irritants.

The prior art drug delivery systems (gel, cream, ointment, powder and microcapsule) suffer a practical problem : their even application or removal to and from the target site requires gentle manipulation and is too time-consuming for treatment of a large number of trauma patients in emergency cases. To overcome this problem, gauze dressings impregnated with a suspension of antibiotics (e.g., fusidic acid and Neomycin) in appropriate media (e.g., petroleum jelly and lanolin) have been developed. However, this delivery system does not control the release of drugs and thus does not solve the allergy or toxicity problems. Furthermore, the dressings impregnated with gel or liquid do not absorb the exudate, and may not provide sufficient breathability which may be desired for the treatment.

The invention is intented to provide a remedy to be above problems. It solves the problem of providing forms of dressings which can adsorb physiologically- or biologically- active compounds which can be released, in a controlled manner, to effect their biological or physiological activity. This invention thus provides a wound or burn dressing which consists of a substrate comprising a physiologically- or biologically- active substance or agent bound, e.g. adsorbed therein, characterized in that the said substrate

has ion-binding sites thereon e.g. by being chemically- modified and further characterized in that the said active substance is in its ionic form ; whereby, upon contact with body exudate from a wound or burn to which such dressing is applied, the physiologically- or biologically- active substance is released in a controlled manner, e.g. in tempo with the formation of exudate, by ion exchange with ion in the body exudate. This controlled release thus reduces unnecessary exposure of unwounded skin surface to the physiologically- or biologically- active agent.

The substrate has anion-binding sites, is a dialkylaminoalkyl cloth and is selected from the group which consists of a dimethylaminomethyl cloth, a diethylaminoethyl cloth, a diethylaminomethyl cloth, a dimethylaminoethyl cloth, a dimethylaminopropyl cloth and a diethylaminopropyl ; preferably diethylaminoethyl cloth ; or it has cation-binding sites, is a carboxyalkyl cloth, and is selected from the group which consists of a carboxymethyl cloth, a carboxyethyl cloth and a carboxypropyl cloth ; preferably a carboxymethyl cloth.

The physiologically-active of biologically- active substance is selected from the group which consists of an antibacterial agent, an antifungal agent, an analgesic agent, a tissue healant agent, a local anesthetic agent, an antibleeding agent, an enzyme, or a vasoconstrictor or a salt form thereof.

Where the substrate is a dialkylaminoalkyl cloth, i.e. a cloth having anion-binding sites, the physiologically- or biologically- active agent is an anionic drug. Such anionic drug may be : an antibacterial, e.g. fusidic acid, pseudomonic acid, ceftriaxone or nafcillin ; or an antifungal, e.g. ciclopirox, nystatin, or undecylenic acid : or an analgesic, e.g. salicylic acid, salicylsulfuric acid or nicotinic acid ; or an antibleeding agent, e.g. adenosine diphosphate, such antibleeding agents operating by making platelets sticky, an initial step required for the stopping of bleeding. Such physiologically- or biologically- active agents may be used in the form of their salts.

Further specification of some of the above-described anionic drugs are as follows :

1. Fusidic Acid is also known as (Z)-16β-(Acetyloxy)-3α,11α-dihydroxy-29-nor-8α,9β,13α, 14β-dammara-17(20), 24-dien-21-oic acid. Its sodium salt, sodium fusidate, is also known as ZN 6.

2. Nafcillin is also known as 6-(2-Ethoxy-1-naphthamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylic acid ; 6-(2-ethoxy-1-aphthamido) penicillanate. The sodium salt is also known as Naftopen and Unipen.

3. Nystatin is also known as Fungicidin.

4. Undecylenic Acid, also known as 10-Undecenoic acid.

5. Salicyclic Acid is also known as 2-Hydroxybenzoic acid.

6. Salicylsulfuric Acid is also known as 2-(Sulfooxy)- benzoic acid.

7. Nicotinic Acid is also known as 3-Pyridinecarboxylic acid.

8. Adenosine Diphosphate is also known as Adenosine 5′-(trihydrogen diphosphate).

Where the substrate is a carboxyalkyl cloth, i.e. a cloth having cation-binding sites, the physiologically- or biologically- active agent is a cationic drug. Such cationic drug may be : an antibacterial, e.g. chlorhexidine, chlorhexidine digluconate, Bacitracin, Chlortetracycline, Gentamycin, Kanamycin, Neomycin, Neomycin B, Paromomycin, Polymyxin, Polymyxin B, Streptomycin, or Tetracycline ; or an antifungal, e.g. Amphotericin B, Clotrimlazole, Miconazole or Natamycin ; or tissue healants, e.g. cysteine, glycine or threonine ; or local anesthetics, e.g. Lidocaine or Pramocaine ; or enzymes, e.g. trypsin, Streptokinase, plasmin (Fibrinolysin) or Streptodomase ; or deoxyribonuclease ; or a cationic vasoconstrictor, e.g. epinephrine or serotonin. Such physiologically- or biologically- active agents may be used in the form of their salts.

Further specification of some of the above-described cationic drugs are as follows:

1. Chlorhexidine is also known as N,N″-Bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide. Its gluconate is known as Hibiscrob.

2. Bacitracin is also known as Ayfivin.

3. Chlortetracycline is also known as 7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11,-dioxo-2-naphthacene carboxamide.

4. Gentamycin includes Gentamicin C_{1a}•, which is also known as O-3-Deoxy-4-C-methyl-3-(methylamino)-β-L-arabinopyranosyl-(1→6)-O[2,6-dramino-2,3,4,6-tetradeoxy-α-D-erythro-hexo pyranosy 1-(1→4)]-2-deoxy-D-streptamine and as gentamicin D.

Gentamicin A is also known as O-2-Amino-2-deoxy-α-D-glucopyranosyl-(1→4)-O-[3-deoxy-3-(methylamino)-α-D-xylopyranosyl-(1→6)]-2-deoxy-D-streptamine.

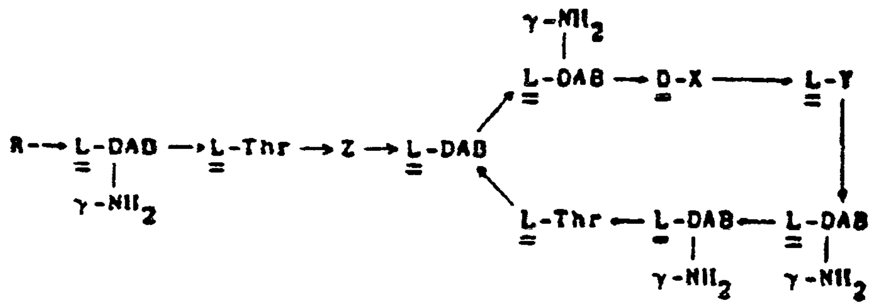
The C complex sulfate is also known as Cidomycin.

5. Kanamycin includes: Kanamycin A sulfate, also known as Cantrex; Kanamycin B, is also known as NK 1006; and Kanamycin B sulfate, also known as Kanendomycin.

6. Neomycin is also known as Mycifradin. It also includes Neamine, which includes: Neomycin A, and Neomycin B, which is also known as Framycetin. Neomycin B sulfate is also known as Fraquinol.

7. Paromomycin is also known as O-2,6-Diamino-2,6-dideoxy-β-L-1-dopyranosyl-(1→3)0-β-ribofuranosyl-(1→5)-O-[2-amino-2-deoxy-α-D-glucopyranosyl-(1→4)]-2-deoxystreptamine. Its sulfate is also known as 1600 Antibiotic.

8. Polymyxin, having the structural formula



(where DAB = α,γ-diaminobutyric acid)
includes:
Polymyxin B, which is a mixture of polymyxins B_1 and B_2;
Polymyxin B sulfate, which is also known as Aerosporin;
Polymyxin B_1, where, in the above Formula, R = (+)-6-methyloctanoyl, X = phenylalanine, Y = leucine, and Z = L-DAB;
Polymyxin B_1 hydrochloride;
Polymyxin B_2, where, in the above Formula R = 6-methylheptanoyl, X = phenylalanine, Y = leucine, and Z = L-DAB;
Polymyxin D_1, where, in the above Formula R = (+)-6-methyloctanoyl, X = leucine, Y = threonine, and Z = D-serine;
Polymyxin D_2, where, in the above Formula R = 6-methylheptanoyl,, X = leucine, Y = threonine, and Z = D-serine; and
Polymyxin E, which is also known as Colistin.

9. Streptomycin is also known as O-2-Deoxy-2-(methylamino)-α-L-glucopyranosyl-(1→2)-O-5-deoxy-3-C-formyl-α-L-lyxofuranosyl-(1→4)-N,N′-bis(aminoiminomethyl)-D-streptamine. Its sesquisulfate is also known as streptomycin sulfate. Streptomycin B is also known as Mannosidostreptomycin.

10. Tetracycline is also known as 4-(Dimethylamino)-1,4-4a,5,5a,6,-11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,-11-dioxo-2-naphthacenecarboxamide. Its phosphate complex is also known as Panmycin Phosphte. Its lauryl sulfate is known as Lauracycline.

11. Amphotericin B is also known as Fungizone.

12. Clotrimazole is also known as 1-[2-Chlorophenyl)-diphenyl-methyl]-1H-imidazole.

13. Miconazole is also known as 1-[2-(2,4-Dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-1H-imidazole. Its nitrate is also known as R-14889.

14. Pimaricin is also known as Tennecetin.

15. Cysteine, Cys (IUPAC abbrev.) is also known as OL-cysteine.

16. Glycine, Gly (IUPAAC abbrev.), is also known as aminoacetic acid.

17. Threonine, Thr (IUPAC abbrev.), is also known as 2-amino-3-hydroxybutyric acid.

18. Lidocaine is also known as 2-(Diethylamino)-N-(2,6-dimethylphenyl)acetamide.

19. Pramocaine is also known as 4-[3-(4-Butoxyphenoxy)-propyl]morpholine.

20. Fibronolysin is also known as Plasmin.

21. Epinephrine is also known as 4-[1-Hydroxy-2-(methylamino)-ethyl]-1,2-benzenediol.

22. Serotonin is also known as 3-(2-aminoethyl)-1H-indol-5-ol; 5-hydroxytryptamine.

The synthesis and characterization of DEAE and CM derivatives of polysaccharides, e.g. cellulose, dextran, and starch are well-documented. The derivatives are non-toxic, non-allergenic and have been used as food additives or pharmaceuticals. Although these derivatives are provided in fiber, powder or granular forms, cloth forms of the derivatives are not commercially available. The cloth forms have definite

advantages in large-scale purification and immobilization of ionic macromolecules (e.g., enzymes) because they provide easy handling (washing, transfer and removal) and faster flow in a packed bed operation. High degrees of derivatization of the cotton cloth tend to either stiffen the fabric texture or reduce the fabric strength. Furthermore, the edges of the woven fabric tend to ravel after modification. Cotton surgical dressing or gauze suffer even greater textural changes.

For topical application, pliability, softness and low linting of dressings are desired. It has been found by the present applicants that modification of nonwoven cellulose-polyester blend fabrics produces suitable ionic dressings. Unmodified, nonwoven cellulose fabrics are commercially available. For example, rayon/polyester non-woven fabric blends (known by the Trade Marks SONTARA 8801 and SONTARA 8407) may be used. They are free of chemical additives (e.g. resins), binder and finish (which would interefere with modification); are soft, pliable and low linting; and have nonravelling edges and good absorbency. Because of the polyester part, the fabric strength is less affected by modification than cellulose fabrics. The apertured style (known by the Trade Mark SONTARA 8407) has been used as medical dressings, because of greater breathability.

Currently available methods for DEAE and CM derivation are aimed for modifying fibers or beads of polyhydroxy polymers and often require stirring and heating for relatively short periods of time. Since efficient stirring and rapid heating are difficult for modification of these fabrics in large sizes and quantities, processes have been devised by the present applicants as will be more fully described hereinafter which allow modification without stirring and at near ambient temperatures

The invention is described hereinafter as carried out with non-woven cloth, but is is to be understood this is by no means any limitative effect since the same method can be carried out with woven cloth.

For DEAE, the nonwoven rayon/polyester cloths are placed on a flat polyethylene sheet and wetted with diethylaminoethyl chloride solution (e.g., 20%) in H_2O and then saturated with NaOH solution (e.g., 15%) saturated with Na_2SO_4. For CM, the cloths placed on a polyethylene sheet are saturated with a sodium monochloroacetate solution (e.g. 20%) in a NaOH solution (e.g. 15%).

Another polyethylene sheet is placed on top of the so-treated cloths. The sandwiched cloths are incubated at 30 °C. for suitable lengths of time (normally less than 2 h). The DEAE cloths are washed with H_2O, 0.5 N NaOH and H_2O. The CM cloths are washed with H_2O, 0.5 N HCl and H_2O. Both types of cloths are air-dried. The degree of modification is controlled by time and the modified cloths must have good adsorption capacity (measured by adsorption of bovine serum albumin) and pliability and softness for contact with skin. Adsorption of fusidic acid to DEAE cloth and chlorohexidine to CM cloths has been used as model systems. The modification reaction can be carried out at any temperature between 20 °C. and 50 °C.

A dialkylaminoalkyl cloth other than DEAE-cloth or a carboxyalkyl cloth other than CM-cloth may be prepared in the same way as generally described above by the use of the corresponding dialkylaminoalkyl halide or by the use of a corresponding salt of a monohalocarboxylic acid.

The physiologically- or biologically- active agent can be adsorbed in the dialkylaminoalkyl or in the carboxyalkyl cloth by soaking the respective cloth in an aqueous or aqueous alcoholic solution of the active agent.

The following are Preparation Example 1 for the preparation of DEAE- and CM- cloths and Examples 2 - 4, which are embodiments of drug cloths of aspects of this invention.

Preparation Example 1, Preparation of DEAE- and CM- cloths

Nonwoven rayon/polyester blend (70/30) fabric (SONTARA 8407 from E.I. DuPont de Nemours and Co.) was used to prepare DEAE-and CM- cloths. This fabric has a unit weight of 5.1 mg per cm^2, and its apertured style permits good aeration when applied to skin.

For DEAE-cloth, the above-described cloth was placed on an alkali-resistant thin plastic sheet (e.g. polyethylene), uniformly moistened with 20% (w/v) diethylaminoethyl chloride hydrochloroide in H_2O (0.04 ml per cm^2 of cloth), and then with 15% (w/v) NaOH in a saturated Na_2SO_4 aqueous solution (0.01 ml per cm^2 of cloth). A second plastic sheet was placed on the top of the cloth. This sandwiched cloth was multiplely layered between two heavy plates (glass, plastic or metal), and incubated at 30 °C. for various lengths of time (e.g. 0.5h. to 2.5 h.). The cloth was then washed with water, then with 0.5 N NaOH, and water (until it had a neutral pH) and then was air-dried.

For CM-cloth, the above-described cloth, placed on a plastic sheet, was uniformly moistened with 20% (w/v sodium monochloroacetate in 15% (w/v) NaOH (0.05 ml per cm^2 cloth) and was then covered with a second plastic sheet. Multiple layers of the sandwiched cloth were incubated as described above for the

preparation of the DEAE-cloth at 30°C. for various lengths of time (e.g. 0.5h. to 3h.). The cloth was then washed with water, then with 0.5N HCL and water (until it had a neutral pH), and then was air-dried.

The degree of cloth modification was measured by adsorption of bovine serum albumin to DEAE-cloth and egg white proteins to CM-cloth. Longer reaction times (at 30°C.) produced a cloth of higher protein adsorption, reaching a maximum adsorption of 5 mg protein per cm² of cloth (1 g protein per/g. cloth). However, overmodification generated undesirable texture (e.g. it was too hard for contact with skin or was too soft for handling). The reaction times of 1.5 h. for DEAE-cloth and 2 h. for CM-cloth were used to obtain suitable pliability and softness (with protein adsorption capacity of 2 mg/cm²).

Examples of the Invention

Example 2. Adsorption of fusidic acid and chlorhexidine

Currently, gauze dressings impregnated with an ointment of fusidic acid or chlorhexidine are used to treat wounds topically. Adsorption of these antibiotics to the ionic dressings according to aspects of this invention was determined. Segments (1 cm square) of DEAE-, CM- and unmodified cloth were soaked in 1.0 ml.cloth segment of 10 mg/ml sodium fusidate or 10 mg/ml chlorhexidine digluconate for 2h. at room temperature. The segments were then washed with water.

Each segment was then soaked in 1.0 ml of porcine serum or Krebs phosphate Ringer to simulate a heavy bleeding situation (at the wound site).

The particular Krebs phosphate Ringer solution used herein had the following composition:

	100 Vol.	0.154 M	NaCl
	4 Vol.	0.154 M	KCl
	3 Vol.	0.110 M	$CaCl_2$
	1 Vol.	0.154 M	KH_2PO_4
	0.5 Vol.	0.154 M	$MgSO_4$
and	0.45 Vol.	0.154 M	$MgCl_2$

The amount of the respective antibiotics released were estimated by standard inhibition zone assay using an Escherichia coli ESS strain as an indicator, and are shown in Table 1.

Table 1. Antibiotics (mg) Released From Ionic Dressings (1 cm²)

	Fusidate from DEAE		Chlorhexidine from CM	
Elution time (h.)	Serum	Ringer Solution	Serum	Ringer Solution
0.5	0.25	0.5	0.1	0.25
1.5	0.5	0.5	0.25	0.3
24	0.63	0.75	1.0	-

Table 1 shows that the serum gradually released both antibiotics from the ionic dressings. The Ringer solution more rapidly released similar amounts of antibiotics. Since the release is due to ion exchange, macromolecular ions in the serum do not seem to be as efficient as inorganic ions in the Ringer solution. The unmodified cloth (similarly treated with the antibiotics) released negligibly small amounts of fusidate and less than a tenth the amounts of chlorhexidine released by the CM dressing.

The air-dried antibiotic dressings were stored in a light-free container at room temperature. After 4 months, the activities of the antibiotics released by the serum were determined. Both the fusidate and the

chlorhexidine dressings exhibited nearly the original activity of antibiotics as described above.

Example 3. Adsorption of other drugs

Segments (1 cm square) of DEAE- and CM- cloth were soaked in 1.0 ml of 10 mg/ml of a variety of topical drugs for 2 h. at room temperature, washed with water, and then soaked in 1 ml of Krebs Ringer phosphate solution for 2 h. at room temperature. The amount of drugs released after 2 h. were estimated by ultraviolet absorption (at wavelengths between 200 to 260 nm) after diluting the extract to linear concentration vs. absorption ranges.

Table 2 (below) illustrates that all the anionic drugs tested adsorbed to the cationic DEAE-cloth, that all the cationic drugs tested adsorbed to the anionic CM-cloth, and that the adsorbed drugs can be extracted by Krebs Ringer phosphate solution. However, the results shown in Table 2 represent the amounts released with a limited volume of the Ringer solution for 2 h. and do not represent maximum adsorption of drugs.

Table 2. Drug Released Into 1 ml Krebs Ringer Solution

Cloth	Drug	Solvent for drug adsorption	Drug released Ringer (mg)
DEAE			
	Sodium Fusidate	H_2O	0.52
	Pseudomonic acid	Methanol	0.33
	Sodium Ceftriaxone	H_2O	0.5
	Nafcilin	"	0.36
	Adenosine diphosphate	"	0.76
	Nystatin	Methanol	0.2
	Undecylenic acid	H_2O	0.2
	Salicylic acid	Methanol	0.25
	Salicylsulfuric acid	H_2O	0.25
	Nicotinic acid	"	0.28
CM			
	Chlorhexidine digluconate	H_2O	0.31
	Bacitracin	"	0.72
	Chlortetracycline	"	0.48
	Gentamycin sulfate	"	0.44
	Kanamycin sulfate	"	0.71

Table 2. (contd) Drug Released Into 1 ml Krebs Ringer Solution

Cloth	Drug	Solvent for drug adsorption	Drug released Ringer (mg)
CM			
	Neomycin B sulfate	"	0.24
	Polymyxin B sulfate	"	0.25
	Streptomycin sulfate	"	1.0
	Tetracycline	Methanol	0.012
	Amphotericin B	"	0.02
	Clotrimazole	"	0.02
	Micronazole	"	0.01
	Cysteine	H_2O	0.12
	Glycine	"	2.0
	Threonine	"	3.0
	Lidocaine	"	0.72

In the above Table, the tests were conducted as follows:

A 1 cm square segment of the ionic cloth was soaked in 1 ml of 10 mg/ml of each drug dissolved in either H_2O or methanol (as noted) for 2 h. at room temperature. The washed segment was soaked in 1 ml of the Ringer solution for 2 h. at room temperature. The released drugs were measured spectrometrically.

Example 4. Adsorption of trypsin and plasmin

Trypsin is capable of removing proteinaceous material from a wound. It is positively charged at a neutral pH, and therefore should be adsorbed to anionic CM-cloth. A 1 cm square segment of CM-cloth was soaked in 1 ml (per segment) of 1 mg/ml trypsin in 0.02 M sodium phosphate buffer (pH 7.0). The segment was washed with water, suspended in 1 ml of the Ringer solution, and assayed for trypsin activity. One segment of the cloth having trypsin absorbed therein showed 150 BAEE units.

Plasmin (or fibrinolysin) occurs in blood and is responsible for fibronolysis, *i.e.* dissolution of blood clots by the proteolytic degradation of fibrin to soluble peptides. A 1 cm square segment of DEAE-cloth was soaked in 1 ml (per segment) of 0.4 mg (1.3 U.)/ml of plasmin (plasminogen activated by streptokinase) solution. The segment was washed with water and suspended in a standard clot for activity to lyse the clot. One segment of the cloth to which plasmin was adsorbed, showed 1 U. activity.

Way In Which the Invention is Capable of Exploitation by Industry

By embodiments of the present invention, dialkylaminoalkyl, preferably diethylaminoethyl (DEAE), and carboxyalkyl, preferably carboxymethyl (CM), forms of dressings have been provided so that anionic drugs can be adsorbed onto DEAE-dressings and cationic drugs onto CM-dressing. Most of proteases are positively charged and thus can be adsorbed to CM-dressing. Thus ionic forms of dressing have been

provided to which a variety of ionic drugs (antibiotics, healants, anesthetics, etc.) as well as enzymes can be adsorbed. When applied on weeping wounds or burns, the drug will be released in controlled amounts by ion exchange with ions in the body exudate in proportion to the amount of exudate. Such a controlled release will reduce unnecessary exposure to drugs and thus to allergic reactions. The fibrinolytic enzymes can be adsorbed to the ionic dressing and may be used to dissolve fibrous or purulent accumulation and reduce inflammation. Ionic irritants generated will be adsorbed to the dressings. Use of these dressings will permit rapid and gentle application and removal of drugs and thus facilitate treatments in emergency situations, e.g. accidents, earthquakes, fires and wars.

The drug dressings of aspects of this invention can also be used to treat skin diseases, e.g., acne, or inflamation. They may also find the same applications as cosmetics, as was dis closed for the micro-spheres, patented by Advanced Polymer Systems, as U.S. Patent No. 4,690,825, as was described in the March 9, 1988 issue of Chemical Week.

Immobilized (adsorbed) enzymes can be used as adjuncts to antibiotic prophylaxis of surgical wounds as well as infected wounds as they show an anti-inflammatory activity. CM dressing should also adsorb cationic irritants, e.g. amines which may be generated from enzyme hydrolysis or infection. These materials can be removed with the dressing. Furthermore, CM dressing will likely adsorb a large amount of fluid and also exhibit a blood coagulating activity.

Another expected advantage of these drug systems is that the adsorbed drugs will be more stable than free drugs either in solution or suspension. Unlike dressings impregnated with drug ointments, the ionic dressings, when applied in dry forms, adsorb fluid weeping from the damaged tissues and provide better air circulation (breathability) which is often desired for the wound treatment.

It has been found that the adsorbed drugs are elutable with porcine serum and with Ringer solution and the eluted drugs have been shown to inhibit the growth of Escherichia coli. This suggests that upon application to weeping sites the dressings are capable of releasing drugs by ion exchange with ions in the blood.

Claims

1. A wound or burn dressing which consists of a substrate comprising a physiologically -or biologically-active substance adsorbed therein, characterized in that the said substrate has ion-binding sites thereon and further characterized in that the said active substance is in its ionic form ; whereby, upon contact with body exudate from a wound or burn to which such dressing is applied, the physiologically- or biologically- active substance is released in a controlled manner by ion exchange with ion in the body exudate.

2. The wound or burn dressing of claim 1, characterized in that said substrate has anion-binding sites and is a dialkylaminoalkyl cloth.

3. The wound or burn dressing of claim 2, characterized in that said dialkylaminoalkyl cloth is selected from the group which consists of a dimethylaminomethyl cloth, a diethylaminoethyl cloth, a diethylaminomethyl cloth, a dimethylaminoethyl cloth, a dimethylaminopropyl cloth and a diethylaminopropyl ; preferably diethylaminoethyl cloth.

4. The wound or burn dressing of claim 1, characterized in that said substrate has cation-binding sites and is a carboxyalkyl cloth.

5. The wound or burn dressing of claim 4, characterized in that said carboxyalkyl cloth is selected from the group which consists of a carboxymethyl cloth, a carboxyethyl cloth and a carboxypropyl cloth ; preferably a carboxymethyl cloth.

6. The wound or burn dressing of claims 1 to 5, characterized in that said physiologically- or biologically- active substance is selected from the group which consists of an antibacterial agent, an antifungal agent, an analgesic agent, a tissue healant agent, a local anesthetic agent, an antibleeding agent, an enzyme or a vasoconstrictor, or a salt form thereof.

7. The wound or burn dressing of claim 2, 3, or 6, characterized in that said physiologically- or biologically- active substance is an anionic drug and is selected from the group which comprises an anionic antibacterial, especially fusidic acid, salts of fusidic acid, pseudomonic acid, ceftriaxone, or nafcillin or salts thereof ; or an anionic antifungal, especially ciclopirox, nystatin, or undecylenic acid, or salts thereof ; or an anionic analgesic, especially salicylic acid, salicylsulfuric acid or nicotinic acid, or salts thereof ; or is an anionic antibleeding agent, especially adenosine diphosphate.

8. The wound or burn dressing of claim 4, 5, or 6, characterized in that said physiologically- or biologically- active substance is a cationic drug and is selected from the group which comprises an cationic antibacterial, especially chlorhexidine, bacitracin, chlortetracycline, gentamycin, kanamycin, neomycin B,

paramomycin, polymyxin B, streptomycin, or tetracycline, or salts thereof ; or a cationic antifungal, especially amphotericin B, clotrimazole, miconazole or natamycin, or salts thereof ; or a cationic tissue healant, especially cysteine, glycine or threonine, or salts thereof ; a cationic local anesthetic, especially lidocaine or pramocaïne, or salts thereof ; or a cationic enzyme, especially trypsin, streptokinase, plasmin (fibrinolysin) or streptodornase, or salts thereof ; or deoxyribonuclease ; or a cationic vasoconstrictor, especially epinephrine or serotonin.

9. The wound or burn dressing of claim 1 to 8, characterized in that said substrate is a non-woven rayon/polyester cloth, preferably in the form of its apertured style.

10. A method for preparing the wound or burn dressing of claim 1 to 9, characterized it that it comprises chemically modifying by derivatizing a substrate to form ion-binding sites therein and binding thereon a physiologically- or biologically- active substance to be adsorbed therein.

11. The method of claim 10, characterized in that said physiologically- or biologically- active substance is bound to said modified substrate by soaking this derivatized substrate in an aqueous or aqueous alcoholic solution of said physiologically- or biologically- active substance.

12. The method of claim 10 or claim 11, characterized in that said substrate is modified to form anion-binding sites therein by means of a dialkylaminoalkyl halide, preferably a diethylaminoethyl chloride solution.

13. The method of claim 10, characterized in that said substrate is modified to form cation-binding sites therein by means of a salt of monohalocarboxylic acid, preferably a sodium monochloroacetate solution.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 40 2820

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,A	US-A-3 817 702 (W. PAULUS et al.) ---		A 61 L 15/03
A	GB-A-2 007 096 (EXTERMA-GERM PRODUCTS) ---		
D,A	US-A-4 585 652 (L.L. MILLER et al.) -----		
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			A 61 L

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	04-07-1989	ESPINOSA Y CARRETERO M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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